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Year: 2019

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## **Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants**

Haslbeck, Friederike B ; Karen, Tanja ; Loewy, Joanne ; Meerpohl, Joerg J ; Bassler, Dirk

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DOI: <https://doi.org/10.1002/14651858.cd013472>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-182095>

Journal Article

Published Version

Originally published at:

Haslbeck, Friederike B; Karen, Tanja; Loewy, Joanne; Meerpohl, Joerg J; Bassler, Dirk (2019). Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants. Cochrane Database of Systematic Reviews, 11:CD013472.

DOI: <https://doi.org/10.1002/14651858.cd013472>



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## **Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants (Protocol)**

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Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants.  
*Cochrane Database of Systematic Reviews* 2019, Issue 11. Art. No.: CD013472.  
DOI: [10.1002/14651858.CD013472](https://doi.org/10.1002/14651858.CD013472).

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[Intervention Protocol]

# Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants

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**Editorial group:** Cochrane Neonatal Group

**Publication status and date:** New, published in Issue 11, 2019.

**Citation:** Haslbeck FB, Karen T, Loewy J, Meerpohl JJ, Bassler D. Musical and vocal interventions to improve neurodevelopmental outcomes for preterm infants. *Cochrane Database of Systematic Reviews* 2019, Issue 11. Art. No.: CD013472. DOI: [10.1002/14651858.CD013472](https://doi.org/10.1002/14651858.CD013472).

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

We will assess the overall efficacy of auditory stimulation for physiological and neurodevelopmental outcomes in preterm infants (< 37 weeks' gestation), compared to standard care. In addition, we will determine specific effects of various musical and vocal interventions for physiological, anthropometrical, social-emotional, neurodevelopmental short- and long-term outcomes in preterm infants, parental well-being, and bonding.

## BACKGROUND

Approximately 15 million infants are born preterm each year, constituting more than 10% of all infants born worldwide (March 2012). Advances in technology and treatments have increased survival rates and reduced morbidity in preterm infants. However, preterm birth interferes with normal brain maturation, and subsequent clinical events and interventions may have additional deleterious effects (Stoll 2015; Webb 2015). Therefore, various non-pharmacological, therapeutic or individual developmental care interventions have emerged, that aim to improve health outcomes and quality of life for both preterm infants and their parents (Symington 2006). Music as therapy is one such intervention, and is used increasingly in neonatal intensive care units (NICU). This has been studied in both observational and experimental designs (van der Heijden 2016).

The sense of fetal hearing has been shown to develop as early as 16 weeks' gestation (Hepper 1994). Auditory perception has already developed when preterm infants are born. Studies suggest that the fetus responds to sound at least as early as 25 weeks to 27 weeks of gestational age (Clark-Gambelunghe 2015; Hepper 1994; Monson 2018). Intrauterine sounds encompass characteristics of organized sound that are highly musical in nature. Maternal heartbeat, for instance, is rhythmic, and the fetus primarily hears the musical parameters of speech: melody, rhythm, prosody (patterns of stress and intonation), phonemes (sounds that distinguish one word from another) and pitch contour of the maternal voice and external voices (Moon 2013; Partanen 2013; Philbin 2017). Music promotes neuronal activation, and many researchers suggest that musical learning starts prior to birth (Huotilainen 2010; Perani 2010). In preterm birth, the enclosed intrauterine environment optimal for fetal growth and maturation is abandoned too early. Aside from other stressful experiences, such as separation from the mother, preterm infants must also adjust to the unusual - and potentially noxious - sound environment of an intensive care unit (Kuhn 2013; Park 2014; Rossetti 2013).

Appropriate auditory stimulation and social contact for preterm infants is desirable (Anderson 2018). Music as therapy may provide environmental and emotional enrichment through meaningful auditory stimulation and social contact (Anderson 2018; Haslbeck 2018; Loewy 2015; Shoemark 2015). This may be particularly warranted following preterm birth, as preterm infants are at risk of neurodevelopmental impairment, parents are at risk of post-traumatic stress disorders and both parents and preterm babies risk bonding difficulties (Borghini 2006; Forcada-Guex 2006; Korja 2011). However, the precise effects of various musical and vocal stimulation types on short- and long-term outcomes in preterm infants and their parents remain ambiguous.

### Description of the condition

Preterm birth is a significant determinant of neurodevelopmental delay, and resulting impairment can have adverse long-term health effects (Pierrat 2017). It is sometimes associated with negative quality of life consequences, and an increased financial burden for the family and healthcare system (EFCNI 2011). Preterm infants face a range of morbidities, such as bradycardia, apnoea, anaemia, and respiratory distress syndrome. These infants are at risk of brain injury, and may have reduced white- and grey-matter volumes (Inder 2005). Such brain-structure abnormalities are associated with long-term neurodevelopmental impairments, includ-

ing motor dysfunction, cerebral palsy, cognitive and behavioural problems, and deficits in executive function (Woodward 2006). Factors such as environmental noise and sensory deprivation (e.g. the lack of the regular intrauterine rhythms of the maternal heartbeat and the maternal voice) may also impact neurodevelopment negatively (Lahav 2014; McMahon 2012; Neville 2002). For many parents, preterm birth is a traumatic and lasting experience. They struggle with numerous problems and concerns, such as the uncertainty of the infant's future, feelings of fear, guilt, loss, grief, and confusion (Flacking 2007; Jotzo 2005; Roque 2017). These reactions may increase parental stress, adversely affect the stress-coping behaviour of their infant, and impair formation of a secure attachment (Borghini 2006; Forcada-Guex 2006; Korja 2011).

### Description of the intervention

Various musical and vocal interventions have been evaluated for efficacy in preterm infants (Haslbeck 2012; van der Heijden 2016). They can be directed towards the infant (with or without parental involvement), to an entire family, or even applied within the whole NICU. The interventions aim to relax, stabilize and stimulate the infant and their parents (Hanson-Abromeit 2008).

Auditory stimulation for preterm infants and their parents incorporates calm music sung softly or played on an instrument. Examples include: lullabies; improvised music; popular, New Age, classical or family indigenous music; songs or sounds entrained to infant vital signs (i.e. synchronized with breathing or heart rate pattern) or based on the acoustic intrauterine environment (womb sounds, heartbeats and parents' voices) (Hanson-Abromeit 2008; Haslbeck 2012; Loewy 2013; Mondanaro 2016). Music therapists, parents, nurses, doctors, nurses and other healthcare professionals deliver the specific stimulation to the infants (and sometimes to their parents). These interventions are provided in addition to standard care in the NICU, and are either performed live or recorded.

### How the intervention might work

The quality of early auditory experiences may have a direct influence on the plasticity of the brain's auditory regions, and may affect cortex development in infants (Yan 2003). Both auditory overstimulation and sensory deprivation in the NICU may adversely affect preterm infants' short- and long-term neurobehavioural development, as the infants are already susceptible to neurodevelopmental impairment (Pineda 2014; Wachman 2011). Studies at the interface of music science and neuroscience suggest that music might promote neurobiological processes in humans, including the modulation of synaptic plasticity (linked to learning and memory), and might facilitate the differentiation, activation, readjustment and growth of neurons (Abbott 2002; Rickard 2005; Sacks 2007). For instance, music can alter brain activity in core structures involved in processing emotions (Koelsch 2014). Auditory stimulation, therefore, is recommended to enhance psychological and physiological health in preterm infants (Jobe 2014; Shoemark 2015).

Several systematic reviews suggest that musical and vocal interventions may have beneficial effects on preterm infants' behavioral states, physiological parameters, sleep quality, oral feeding, and pain (Anderson 2018; Hartling 2009; Haslbeck 2012; Hodges 2010; Standley 2012; Tramo 2011; van der Heijden 2016). For example, a systematic review of 1128 participants in 20 randomised control trials (with at least 10 participants per group) looked at live or recorded music interventions, but excluded studies that used speech, nat-

ural sounds or womb sounds (van der Heijden 2016). Due to incompleteness and heterogeneity of data, the authors did not conduct any meta-analyses. The van der Heijden 2016 review suggested that music may improve heart rate, sleep, feeding and sucking outcomes in preterm infants. A meta-analysis by Bieleninik 2016 could not confirm or refute beneficial effects on those outcomes, but did find a favourable impact of music on the infants' respiratory rate, and additionally demonstrated a reduction of maternal anxiety. These meta-analyses included only randomised control trials with music therapist involvement (carried out by or in consultation with a certified or trained music therapist) (Bieleninik 2016).

## Why it is important to do this review

A number of systematic reviews have demonstrated ambiguous results for the efficacy of various types of auditory stimulation on preterm infants. Most of the reviews focused on a specific topic (e.g. maternal voice (Krueger 2010); music (Hartling 2009); or music interventions carried out by or in consultation with a trained music therapist (Bieleninik 2016)). The authors of these reviews concluded that the heterogeneity and clinical diversity of the included studies prevented the drawing of definite conclusions about the impact of auditory stimulation on preterm infants (Hartling 2009; Haslbeck 2012; Hodges 2010; Krueger 2010; Standley 2012; van der Heijden 2016). Therefore, a more comprehensive and rigorous systematic review is needed to address existing controversies arising from apparently conflicting studies and reviews. Firstly, we will evaluate the overall efficacy of auditory stimulation. Then, by analysing the impact of various types of auditory stimulation systematically with subgroup analysis, and by focusing on the methodological quality of the included studies, we may be able to provide better guidance. We may be able to determine how to use these interventions most effectively to promote specific outcomes in preterm infants and their parents (e.g. live versus recorded versions; sung versus instrumental; choices made in rendering decisions regarding length and time of intervention, associated keys, etc.). The current review should assist health professionals in neonatal care to make practical, evidence-based decisions about the use of musical and vocal interventions for preterm infants and their parents. If such a low-cost, low-risk intervention is demonstrated to be effective in supporting preterm infants' neurodevelopment and parental well-being, the findings could have significant clinical implications for this vulnerable patient population.

## OBJECTIVES

We will assess the overall efficacy of auditory stimulation for physiological and neurodevelopmental outcomes in preterm infants (< 37 weeks' gestation), compared to standard care. In addition, we will determine specific effects of various musical and vocal interventions for physiological, anthropometrical, social-emotional, neurodevelopmental short- and long-term outcomes in preterm infants, parental well-being, and bonding.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include parallel, cluster and factorial randomised controlled trials in the review. We will include the first phase of any cross-over trials for short-term outcomes only, to avoid bias by carry-over effects.

#### Types of participants

We will include preterm infants of less than 37 weeks' gestational age, during hospitalisation. We will include parents only when they are involved in the musical or vocal intervention (listening to it with their infant, or providing it for their infant or themselves, in relation to their infant, e.g. to support singing to their infant).

#### Types of interventions

We define the intervention to include any musical or vocal stimulation. The intervention can be provided live or be a recording. It can address either the infant alone or also the parents. The music intervention can be combined with another intervention, such as skin-to-skin care, but only if both arms of the study receive the additional intervention. We will include studies that examined a combination of interventions versus only music or voice. Also studies that compare one type of music or voice to another type of music or voice will be included and analysed separately. Music interventions during painful procedures will be included, and analysed separately. A parent, music therapist, musician, doctor, nurse, or other health professional or caregiver can deliver the intervention. The intervention should include either musical elements, such as rhythm and melody, or sounds based on the acoustic intrauterine environment, e.g. womb sounds, heartbeats, and the human voice.

The intervention should last at least five minutes and occur at least three times to be included in the review. The intervention period may include any time from birth to hospital discharge. We will compare the interventions with standard care without musical or vocal stimulation. We will exclude auditory stimulation with white noise (noise with constant amplitude throughout audible frequency range) or digital signals. These stimulation types lack musical parameters such as melody and prosody.

#### Types of outcome measures

##### Primary outcomes

Primary short-term outcome in preterm infants:

- change in mean oxygen saturation before and after the intervention.<sup>a</sup>

Primary long-term outcome in preterm infants:

- Bayley Scales of Infant and Toddler Development (BSID-II and III),<sup>b</sup> focusing on mean mental development index (MDI) scores and psychomotor development index (PSI) scores at two years of corrected age (Johnson 2008).

Primary outcome for parents:

- change in state anxiety,<sup>b</sup> defined as mean State-Trait Anxiety Inventory Score with 20 items and four-point Likert Scale (Spielberger 1983).

##### Secondary outcomes

Short-term outcomes in preterm infants:

- heart rate: beats per minute<sup>a</sup> (measured by pulse oximetry or electrocardiogram);
- respiratory rate: inspirations per minute<sup>a</sup> (measured by, e.g. electric strain-gauges, thoracic impedance plethysmography, nasal air-flow sensor and spirometers);

- heart rate variability<sup>a</sup> (measured by low-frequency power (ms<sup>2</sup>/Hz); high-frequency power (ms<sup>2</sup>/Hz); low frequency/ high frequency ratio, reflecting the balance between sympathetic and parasympathetic tone);
- behavioural outcomes<sup>b</sup> (measured with behavioural numerical scores or scales for neonates, e.g. Assessment of Preterm Infant Behavior (Als 2005));
- hospitalisation (days);
- adverse effects, including severe apnoea during the intervention requiring stimulation by the neonatal care team; and
- weight gain (kg/day).

Long-term outcomes in preterm infants at five years of age:

- neurodevelopment (assessed by standardized follow-up examinations, e.g. intelligence quotient (Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Park & Demakis 2017); Kaufmann Assessment Battery for Children (K-ABC II) (Melchers 2009)).

Secondary outcomes for parents:

- parental well-being (measured with, e.g. the Edinburgh Postnatal Depression Scale);
- attachment<sup>b</sup> (measured with standardized scales, e.g. Postpartum Bonding Questionnaire (Hoffenkamp 2015)).

<sup>a</sup>Assessed up to 30 minutes before, during and 30 minutes after each musical intervention or control condition; reported at study level as mean changes or assessed after the last measurement round of musical intervention or control condition.

<sup>b</sup>Assessed before and after the whole intervention or control period.

## Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see [the Cochrane Neonatal search strategy for specialized register](#)). We will search for errata or retractions from included studies published in full-text on PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)), and report the date this was done within the review.

## Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2019, current issue) in the Cochrane Library; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1946 to current); PsycINFO (1806 to present); Web of Science (1976 to present); and CINAHL (1981 to current). We will use the following key words: (auditory stimulation, music, voice, song, sound, vocal, singing, womb sounds, heartbeat) along with the standard search of Cochrane Neonatal to translate the search into all databases ([Appendix 1](#)). We will not apply language restrictions.

We will search clinical trial registries for ongoing or recently completed trials. We will search The World Health Organization's International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictip/search/en/](http://www.who.int/ictip/search/en/)) and the U.S. National Library of Medicine's ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)) via Cochrane CENTRAL. Additionally,

we will search the ISRCTN [Registry](#) for any unique trials not found through the Cochrane CENTRAL search.

## Searching other resources

We will seek the reference lists of all included articles and reviews for relevant articles not identified in the primary search. We will seek abstracts from the proceedings of relevant academic meetings, including the Paediatric Academic Societies, the European Society for Paediatric Research, the European Association of Music Therapy, The American Music Therapy Association and the World Federation of Music Therapy.

## Data collection and analysis

We will perform data collection and analysis according to the recommendations of the Cochrane Neonatal Review Group.

## Selection of studies

Two review authors (FH and TK) will independently assess study eligibility for inclusion in the review according to the prespecified selection criteria. They will screen titles and abstracts to remove obviously irrelevant reports. The review authors will link together multiple reports of the same study. They will examine full-text reports to establish the compliance of studies with the eligibility criteria. If trial eligibility is unclear, they will resolve discrepancies through discussion with the other review authors to reach a consensus. We will list all excluded studies with reasons for exclusion. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

## Data extraction and management

Two review authors (FH and TK) will independently conduct data extraction using and adapting the most recent version of the Cochrane data collection form ([Higgins 2011](#)). They will pretest the adapted version with a subset of five studies before general application. They will use the adapted form to decide trial inclusion or exclusion, and to extract data from eligible trials. When data appear to be missing, they will request additional information from authors of the original reports. They will enter and cross-check data using Review Manager 5 software ([Review Manager 2014](#)). If there are disagreements when comparing extracted data, they will resolve them in consultation with the other review authors.

## Assessment of risk of bias in included studies

Two review authors (FH and TK) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool ([Appendix 2](#)) ([Higgins 2011](#)). In cross-over trials they will assess whether the short-term cross-over design is suitable, whether there is a carry-over effect, whether only first period data are available, whether the analysis is correct and whether the results are comparable with those from parallel-group trials. The two authors will resolve discrepancies through discussion with the other review authors to reach a consensus.

## Measures of treatment effect

We will analyse the treatment effects of the individual trials using Review Manager 5 ([Review Manager 2014](#)). For dichotomous data, we will use risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CIs). If the difference between groups is statistically significant, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat



for an additional harmful outcome (NNTH), with their respective CIs. We will evaluate continuous data by assessing the mean difference (MD) with its 95% CI. If studies report the same outcome but measure it in different ways, we will use the standardized mean difference (SMD) with its 95% CI. Where summary statistics are missing, we will derive them from the accompanying P values.

We will analyse short-term cross-over trials if there is no significant risk of a carry-over effect. We will calculate an effect estimate using the generic inverse variance method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will incorporate cross-over trials into meta-analyses using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we identify cluster trials, we will incorporate them using generic variance methods for analysis (Higgins 2011).

### Unit of analysis issues

If the following issues occur, we plan to address them according to the methods described below.

#### Cluster-randomised trials

In cluster-randomised trials, groups of participants rather than individuals are randomised to different interventions. Because of this, participant data can no longer be assumed to be independent of one another. Unfortunately, some cluster-randomised trials are not analysed correctly, i.e. do not take into account that the unit of allocation (the group) is different from the unit of analysis (the individual). If this clustering is ignored there is a unit of analysis error, which means that the resulting P values and 95% CIs will be artificially small and lead to an inappropriately increased weight in the meta-analysis. If cluster-randomised trials fail to report results based on appropriate analyses such as the multi-level model or variance component analysis, we will use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 16.3.3) (Higgins 2011) to re-analyse these trials with appropriate consideration of the intracluster (or intraclass) correlation coefficient (ICC) to estimate the effective sample size. Sensitivity analyses will be performed to explore whether there are any differences in effects between cluster- and individually randomised trial.

#### Cross-over trials

Cross-over trials are suitable for evaluating interventions with a temporary effect in the treatment of stable conditions. The principal problem is that of carry-over (a type of period-by-intervention interaction). Since we believe that some carry-over from period one to period two cannot be precluded in these trials in our setting, we plan to include only the data from the first period (as suggested in chapter 16.4.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)).

#### Studies with more than two intervention groups (multi-arm studies)

If more than one comparison arm from the same trial is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size (e.g. of the control group) so that the same participants do not contribute data to the meta-analysis more than once (i.e. splitting the 'shared' group into two or more groups) according to the methods described in the *Cochrane Handbook for Systematic*

*Reviews of Interventions* (chapter 16.5.4) (Higgins 2011). To reflect the fact that comparisons within multi-arm studies are correlated, we will adjust the standard error of each two-arm comparison from a multi-arm study. We will use the method proposed by Rücker and Schwarzer which uses back-calculated standard errors in the weighted least-square estimator to reflect the within-study correlation (Rücker 2012; Rücker 2014; Rücker 2016).

#### Multiple measurement of outcomes

When primary outcomes are assessed at more than one time point in our time ranges, we will use the data from the latest time point available in our analyses. We do not plan to adjust for multiplicity in our review based on multiple outcome measurements.

#### Dealing with missing data

We will contact the authors whenever we detect that data and statistics are missing or incomplete to request further information. However, when data are missing due to dropouts, we will include the reported infants and examine the effect of losses in a sensitivity analysis according to risk of bias. We will contact the primary investigators. If authors are unable or unwilling to provide the data, we will still include the study in the review and explicitly state that data are missing.

#### Assessment of heterogeneity

We will perform heterogeneity tests, including the  $I^2$  statistic. When the  $I^2$  statistic is higher than 50%, we will assess the source of the heterogeneity by sensitivity and subgroup analysis (Subgroup analysis and investigation of heterogeneity). We will look for evidence of bias or methodological differences between trials.

#### Assessment of reporting biases

For outcomes reported by more than ten studies, we will prepare a funnel plot to assess possible reporting bias.

#### Data synthesis

We will use the standard methods of Cochrane and the Cochrane Neonatal Review Group to perform statistical analysis (neonatal.cochrane.org/resources-review-authors). We will analyse the treatment effects of all infants in the eligible trials. We will use a fixed-effects model to combine the data, since we expect high heterogeneity for most outcomes. We will calculate average estimates of RR and RD with 95% CIs for any meta-analyses. We will use the MD with 95% CIs for continuous outcomes that are measured in the same way between trials. We will calculate the standardized mean difference (SMD) with 95% CIs to combine trials that measured the same outcome but used different scales. We will interpret individual trials separately when a meta-analysis appears to be inappropriate based on clinical judgement and the  $I^2$  heterogeneity test (i.e. when  $I^2 > 80\%$ ).

#### Certainty of the evidence

We will use the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence (GRADEproGDT). We will include the following seven outcomes in the table:

- oxygen saturation;
- respiration rate;



- heart rate variability;
- Bayley Scales of Infant and Toddler Development at two years;
- neurodevelopment;
- parental anxiety; and
- parental well-being.

### Subgroup analysis and investigation of heterogeneity

According to the heterogeneity of auditory stimulation types, we will compare the following modalities separately, if we have a sufficient number of studies.

- Auditory stimulation:
  - spoken voice;
  - sung voice;
  - music without voice;
  - womb sounds;
  - rhythmic sounds; or
  - breathing sounds.
- Auditory stimulation:
  - live, infant-directed or entrained music; or
  - recorded or standardized music.
- Musical decision or selection:
  - \* by parent; or
  - \* random, unidentified or unknown.
- Duration of intervention:
  - \* between five and 10 minutes; or
  - \* more than 10 minutes.
- Frequency of intervention:
  - \* between three and 7 times; or
  - \* at least 8 times.
- Auditory stimulation:
  - \* alone; or
  - \* combined with other interventions (e.g. skin-to-skin care).
- Painful procedure:
  - \* with auditory stimulation; or
  - \* without auditory stimulation.
- Gestational age:
  - extremely preterm (less than 28 weeks' gestation);
  - very preterm (28 to 32 weeks' gestation);
  - moderate to late preterm (32 to 37 weeks' gestation).

Given that studies in a variety of settings may not have reliable gestational age and may therefore use birth weight categories, we will include infants categorized as:

- Low birth weight (LBW) infants – defined as infants with birth weight < 2500 g
- Very low birth weight (VLBW) infants – defined as infants with birth weight < 1500 g
- Extremely low birth weight (ELBW) infants – defined as infants with birth weight < 1000 g

Infants with birth weights 1500 to 2499 g will be grouped with the moderate preterm infants, infants 1000 to 1499 g will be grouped with the very preterm infants, and infants < 1000 g will be grouped with the extremely preterm infants.

We will assess differences between subgroups by using the formal test for subgroup differences in Review Manager 5.1 ([Review Manager 2014](#)).

We will estimate treatment effects in individual trials and examine heterogeneity between trials by inspecting forest plots and quantifying the impact of heterogeneity by using the  $I^2$  statistic, a measure that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error ([Deeks 2017](#)). We will interpret results as follows:

- Less than 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity;
- 75% to 100%: high heterogeneity.

If we detect statistical heterogeneity, we plan to explore possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) by performing post hoc subgroup analyses.

### Sensitivity analysis

We will perform sensitivity analyses where sufficient data are available to explore methodological heterogeneity. It is worthwhile to note that double-blinding will scarcely be possible in intervention designs with live music. Consequently, it is all the more crucial that the outcome assessors are blind to the data. In our sensitivity analyses, we will exclude trials with high risk of bias for any of the following: allocation concealment, adequate randomisation, blinding of outcome assessment ([Schulz 1994](#); [Schulz 2000](#)).

### ACKNOWLEDGEMENTS

We thank Cochrane Neonatal for reviewing this protocol. We acknowledge the use of the standard template used by Cochrane Neonatal.

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## APPENDICES

### Appendix 1. Cochrane Neonatal standard search strategy

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2011). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

#### CENTRAL via CRS Web:

1. MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET
2. infant or infants or infant's or "infant s" or infantile or infancy or newborn\* or "new born" or "new borns" or "newly born" or neonat\* or baby\* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET
3. #2 OR #1

#### MEDLINE via Ovid - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R):

1. exp infant, newborn/
2. (newborn\* or new born or new borns or newly born or baby\* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat\*).ti,ab.
3. 1 or 2
4. randomized controlled trial.pt.
5. controlled clinical trial.pt.
6. randomized.ab.
7. placebo.ab.
8. drug therapy.fs.
9. randomly.ab.
10. trial.ab.
11. groups.ab.
12. or/4-11
13. exp animals/ not humans.sh.
14. 12 not 13



15. 3 and 14
16. randomi?ed.ti,ab.
17. randomly.ti,ab.
18. trial.ti,ab.
19. groups.ti,ab.
20. ((single or doubl\* or tripl\* or treb\*) and (blind\* or mask\*)).ti,ab.
21. placebo\*.ti,ab.
22. 16 or 17 or 18 or 19 or 20 or 21
23. 2 and 22
24. limit 23 to yr="2018 -Current"
25. 15 or 24

#### **CINAHL via EBSCOhost:**

(infant or infants or infant's or infantile or infancy or newborn\* or "new born" or "new borns" or "newly born" or neonat\* or baby\* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

## **Appendix 2. Risk of bias tool**

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomisation, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the 'Characteristics of included studies' table. We will evaluate the following issues and enter the findings into the 'Risk of bias' table..

### **1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?**

For each included study, we will categorize the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

### **2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?**

For each included study, we will categorize the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

### **3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?**

For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

### **4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?**

For each included study, we will categorize the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.



### **5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?**

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorize the methods as:

- low risk (< 20% missing data);
- high risk ( $\geq$  20% missing data); or
- unclear risk.

### **6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?**

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

### **7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?**

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

## **CONTRIBUTIONS OF AUTHORS**

The first author wrote the protocol and all other authors reviewed, commented and completed the protocol.

## **DECLARATIONS OF INTEREST**

FH has no conflicts of interest to declare.

TK has no conflicts of interest to declare.

JL has no conflicts of interest to declare.

JM has no conflicts of interest to declare.

DB has no conflicts of interest to declare.

## **SOURCES OF SUPPORT**

### **Internal sources**

- No sources of support supplied

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**External sources**

- Vermont Oxford Network, USA.

Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.